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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
LARSON,T	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 12/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev 2/95)

1- File Copy

Application No.	Applicant(s)
09/340,595	PODHAJCER ET AL

Office Action Summary

Examiner	Art Unit
Thomas G. Larson, Ph.D.	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *19 October 2000*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18,23-27 and 29-36* is/are pending in the application.

4a) Of the above claim(s) *29-35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-18,23-27 and 36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some * c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4*
18) ☐ Interview Summary (PTO-413) Paper No(s).
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other

1. Applicant's election of the invention of group I, claims 1-18, 23-27, and 36, in Paper No. 8, filed 10/19/00, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 23-27 and 29-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

A reference to parent application PCT/GB97/03548 is required at the beginning of the specification. See MPEP 1895.01(F).

4. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to "Microfiche Appendix" and the drawings, each of the lettered items should appear in upper case, without underlining or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-References to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Microfiche Appendix" (see 37 CFR 1.96).
(e) Background of the Invention.
    1. Field of the Invention.
    2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing (see 37 CFR 1.821-1.825).

5. The disclosure is objected to because of the following informalities: The Brief Description of the Drawings (pp. 10-11) appears to be inserted within the Detailed Description of the Invention (p. 10) rather than being placed between the Brief Summary of the Invention (p. 4) and the Detailed Description of the Invention.

Appropriate correction is required.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 23, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Everitt et al. (document no. AR2 on the PTO-1449 submitted with the information disclosure statement filed 10/28/99).

Claim 23 is drawn to an antisense polynucleotide that binds to and reduces the translation of an osteonectin mRNA. Claims 25-27 are drawn to a plasmid or viral vector that encodes an antisense polynucleotide that inhibits osteonectin.

Everitt et al. disclose expression vectors that express a transcript antisense to the SPARC mRNA (p. 135, ¶ bridging cols. 1 and 2, to first full ¶ of col. 2, and Fig. 1). They also disclose cells transfected with the vector (p. 135, col. 2, 2nd full ¶). SPARC is a synonym for osteonectin, as evidenced by the specification at p. 1, ln. 10.

8. Claims 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,340,934 (document no. AA1 on the PTO-1449 submitted with the information disclosure statement filed 10/28/99).

Claim 23 is drawn to an antisense polynucleotide that binds to and reduces the translation of an osteonectin mRNA. Claim 24 limits the polynucleotide of claim 23 to being DNA.

The '934 patent teach that antisense sequences may be prepared from a group of six different cDNAs (col. 1, lns. 56-61; col. 1, ln. 65-col. 2, ln.3), where each cDNA encodes a different bone matrix protein including osteonectin (Fig. 6 and col. 1, ln. 60). The patent further teaches that the sequences may be prepared in the form of an RNA or DNA polynucleotide (Col. 1, lns. 40-43; col. 1, ln. 65-col. 2, ln. 18). The '934 patent further teaches that the antisense sequences may be used to inhibit the function of the members of the group of bone matrix proteins by inhibiting protein synthesis (col. 7, lns. 5-17, and col. 8, lns. 43-57).

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-18, 23-27, and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 9, 10-13, 18 and 36 are drawn to pharmaceutical compositions comprising a generic inhibitor of osteonectin of unspecified structure, and to methods of treating a tumor in a patient comprising administering a generic

inhibitor of osteonectin of unspecified structure. The claims encompass a compositions or the administration of a composition where the composition comprises an inhibitor that acts on osteonectin activity through a wide range of mechanisms. The claimed subject matter embraces compounds that interact directly with the osteonectin protein to inhibit its activity, compounds that inhibit secretion of the osteonectin protein, compounds that inhibit the transcription of the osteonectin gene or another unspecified gene that regulates osteonectin expression or activity, and compounds that inhibit the translation of osteonectin mRNA either directly or by inhibiting another gene product that regulates translation of osteonectin mRNA. The claims provide only functional limitations and provide no structures that are capable of inhibiting osteonectin. Thus, the subject matter embraced by the claims is drawn to what the inhibitor does rather than what it is.

The specification teaches the inhibition of osteonectin/SPARC expression using antisense sequences targeted to the osteonectin/SPARC mRNA, either provided in the form of an antisense oligonucleotide or an antisense transcript produced by an expression vector. No other compositions for inhibiting osteonectin activity appear to be described. For example, no small molecule inhibitors of osteonectin activity, expression, or secretion are taught. No small molecules that would inhibit a regulator of osteonectin expression, activity or secretion are taught. No antigene (triplex forming) sequences that would inhibit transcription of the osteonectin gene are taught. No ribozyme sequences are taught that would inhibit

expression of the osteonectin transcript. No antisense, ribozyme, or antigene sequences are taught that would inhibit the expression of a regulator of osteonectin expression, activity, or secretion.

Because the description provided in the specification is limited to antisense inhibitors of osteonectin expression that are solely targeted to the osteonectin transcript, the skilled artisan would not be able to determine any other structures capable of inhibiting osteonectin activity based on the disclosure. Based on such a limited description, the skilled artisan would not be able to envisage any additional inhibitors of osteonectin activity beyond antisense sequences directed to the osteonectin transcript and, therefore, would not reasonably conclude that applicant had possession of the invention as claimed at the time the specification was filed.

Claims 1-8, 10-17, 23-27, and 36 all embrace antisense sequences or methods of using antisense sequences targeted to a transcript from a generic osteonectin gene from an unspecified organism. The specification only teaches the sequence of the human osteonectin cDNA (p. 11, ln. 15-p. 12, ln. 7) and an antisense sequence to a human osteonectin cDNA (p. 12, lns. 7-14). No osteonectin sequences are taught for any other species of organism. Since the skilled artisan would not be able to determine the sequence of an osteonectin transcript for any species of organism other than human based on the disclosure, and since the sequence of a transcript is required to determine the sequence of an antisense polynucleotide, the artisan

would not be able to determine antisense inhibitors of osteonectin for species of organisms other than human. Based on such a limited description, the skilled artisan would not be able to envisage any antisense inhibitors of osteonectin activity beyond antisense sequences directed to the human osteonectin transcript and, therefore, would not reasonably conclude that applicant had possession of the invention as claimed at the time the specification was filed.

11. Claims 1-18 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ 2d 1400, 1404; also see *Ex parte Forman*, 230 USPQ 546), the issue of enablement in molecular biology was considered and the factors to be considered in a determination of "undue" experimentation were summarized. These factors include (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of skill of those in the art; (e) the predictability of the art; (f) the amount of direction or guidance presented; (g) the presence or absence of working examples; (h) the quantity of experimentation necessary. See MPEP § 2164.01(a).

Claims 1-4, 9, 10-13, 18 and 36 are broadly drawn to pharmaceutical compositions comprising a generic inhibitor of osteonectin of unspecified structure, and to methods of treating a tumor in a patient comprising administering a generic inhibitor of osteonectin of unspecified structure. The claims provide only functional limitations and provide no structures that are capable of inhibiting osteonectin. Thus, the subject matter embraced by the claims is drawn to what the inhibitor does rather than what it is.

The state of the art is such that only inhibitors of human osteonectin (SPARC) appear to be known (Everett et al.). No other inhibitors of osteonectin appear to be known in the art.

The art appears to be unpredictable. Aside from antisense inhibitors, no structure/function correlation appears to have been established in the art or in the disclosure that would allow the skilled artisan to predict what structures would be capable of inhibiting osteonectin activity. Therefore, the artisan would be required to resort to trial and error experimentation to find additional compounds that could be used to inhibit osteonectin activity. Even if the artisan did find additional inhibitors of osteonectin, it is unpredictable whether or not they would be suitable for use in a pharmaceutical composition or in a therapeutic method.

The level of skill in the art is high with the typical skilled artisan having a Ph.D., and M.D., or both a Ph.D. and an M.D., and also having several years of

postdoctoral-level training. In spite of this high level of skill, the art remains in the undeveloped state described above.

The specification teaches an expressed antisense construct for inhibiting expression of the human osteonectin transcript. No other inhibitors of osteonectin are taught. For example, no small molecule inhibitors of osteonectin activity, expression, or secretion are taught. No small molecules that would inhibit a regulator of osteonectin expression, activity or secretion are taught. No antigene (triplex forming) sequences that would inhibit transcription of the osteonectin gene are taught. No ribozyme sequences are taught that would inhibit expression of the osteonectin transcript. No antisense, ribozyme, or antigene sequences are taught that would inhibit the expression of a regulator of osteonectin expression, activity or secretion.

The specification discloses a working example of an expressed antisense construct for inhibiting expression of the human osteonectin transcript. No additional working examples of inhibitors of osteonectin are disclosed.

The artisan would be required to engage in a significant amount of experimentation to practice the invention as broadly as claimed in view of the fact that the prior art and the disclosure only provide guidance concerning the application of antisense directed to the transcript of the human osteonectin transcript as an inhibitor of osteonectin expression. The required experimentation would include the screening of random compounds for the ability to inhibit

osteonectin activity, and the additional screening of compounds that do inhibit osteonectin activity for suitability as pharmaceutical compositions. Based on the unpredictability of the art and the breadth of the claimed subject matter, the required experimentation would be extensive and of a trial-and-error nature. Such experimentation can not be considered routine in nature.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth *in In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation. See MPEP § 2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging in undue experimentation, the specification fails to provide a disclosure that is commensurate with the scope of the claims.

Claims 1-8 and 36 broadly embrace a pharmaceutical composition comprising a generic antisense oligonucleotide or a generic expression vector that expresses a generic antisense transcript where the antisense oligonucleotide or transcript binds to and inhibits expression of an osteonectin transcript. Claims 10-17 embrace therapeutic methods of treating a tumor comprising the step of administering the above pharmaceutical composition to a patient. Claims 9 and 18 respectively embrace a pharmaceutical composition comprising an antigene oligonucleotide to

inhibit transcription of an osteonectin gene, and the therapeutic application of such a composition to treat a tumor.

With the single exception of the treatment of CMV-associate retinitis by formivirsen (Vitravene), the successful therapeutic application of a pharmaceutical composition comprising an antisense compound unknown in the art at the time the application was filed. For example, Stull et al. teach that the development of nucleic acid therapeutics is impeded by "several formidable obstacles...(that) require improving the stability of polynucleotide drugs in biological systems, optimizing the affinity and efficacy of the drug without reducing its selectivity, and targeting and delivering nucleic acids across cell membranes" (p. 476, col. 1, second full ¶). Stull et al. further state that "the delivery and entry of nucleic acid drugs into the target site remains a major obstacle to the successful introduction of this aspect of the molecular biology revolution into a clinical setting" (p. 478, col. 1 first full ¶). Gewirtz et al. teach that a "major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their targets" (p. 3161, col. 3, lns. 6-10). Rojanasakul teaches that the effective use of oligonucleotide therapeutics "has been limited due to several problems.... (B)ecause of their large size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting and affinity...to the target site pose major challenges to the successful utilization of these compounds" (abstract, lns. 8-13). Jen et al. also teach that the problem of

delivery is one of the major obstacles to the therapeutic application of antisense compounds (p. 131, col. 2, ¶ 2, to p. 314, col. 1, ¶ 3). Jen et al. state that "some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable" (p. 313, col. 2, ¶ 2, last sentence). Jen et al. further state that "(g)iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive" (p. 315, col. 2, lns. 7-9). Formivirsen appears to be a special case with regard to these obstacles: it is delivered by injection directly into the eye (Crooke, p. vii, col. 1, ¶ 2), thereby avoiding many of the problems associated with the effective delivery of an antisense compound to the target tissue in the body.

With regard to the delivery of antisense polynucleotides by an expression vector, Mercola et al. (document no. AT7 on the PTO-1449 submitted with the information disclosure statement filed 10/28/99) state that "(m)ethods for the transduction of a high percentage of target cells ... for the treatment of established tumors are deficient at present" (p54, col. 2, 2nd full ¶). Crystal teaches that obstacles such as inconsistent results, and a lack of suitable vectors have to be overcome before therapies based on gene transfer will be successful (Crystal, p. 409, section titled "What are the Obstacle to Successful Human Gene Transfer?"). The Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, which was released at about the time the application was originally filed, found that "...clinical efficacy has not been definitively

demonstrated at this time in any gene therapy protocol..." and that "(s)ignificant problems remain in all basic aspects of gene therapy" (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, p. 1, items 2 and 3 under "The Panel Finds that"). The panel also emphasizes the lack of suitable vectors and further states that "an inadequate understanding of the biological interaction of these vectors with the host" (p. 1, item 3 under "The Panel Finds that").

Regarding the predictability of the art, the outcome of experiments involving biological or physiological systems is generally regarded as unpredictable. More specifically, the antisense and expression vector arts are unpredictable for the reasons discussed above.

The level of skill in the art is extremely high with the skilled artisan generally having a Ph.D., and M.D., or both a Ph.D. and an M.D., together with several years of postdoctoral research experience. However, in spite of this high level of skill, the therapeutic application of nucleic acids, including antisense polynucleotides, has remained a relatively undeveloped art, as discussed above.

The specification teaches an expressed antisense construct for inhibiting expression of the human osteonectin transcript. No other nucleic acid inhibitors of osteonectin are taught. No antigene (triplex forming) sequences that would inhibit transcription of the osteonectin gene are taught. No ribozyme sequences are taught that would inhibit expression of the osteonectin transcript. No antisense, ribozyme,

or antigene sequences are taught that would inhibit the expression of a regulator of osteonectin expression, activity, or secretion. Additionally, the specification lacks the teachings required to overcome the known obstacles in the art to the successful therapeutic application of antisense nucleic acids discussed above. The specification lacks the guidance required to deliver the osteonectin antisense sequence to the targeted tumor cells in a whole organism, either as an oligonucleotide, or in the form of an expression vector that produces an osteonectin antisense polynucleotide. What guidance is provided is of a cursory nature and does not go beyond what was already known in the art at the time the specification was filed.

The specification discloses a working example of an expressed antisense construct for inhibiting expression of the human osteonectin transcript. No additional working examples of inhibitors of osteonectin are disclosed. This working examples comprises transfixing tumor cells with an expression vector that produces an antisense construct targeted to the osteonectin transcript and injecting the transfected tumor cells into a mouse. This working example is not seen to reasonably correlate with a "method of tumor therapy ... in a patient in need thereof...." because such a method would require an effective method of delivering the expression vector to a pre-existing tumor in a whole animal and the working example does not exemplify such a method. As discussed above, methods for the effective delivery of expression vectors to target cells in a whole animal are not known in the art. The working example also does not reasonably correlate with the

treatment of a tumor using antisense oligonucleotides since avoids the obstacles to the effective deliver of an antisense oligonucleotide to a pre-existing tumor in a whole animal.

Regarding the amount of experimentation, due to the lack of guidance from the art and specification and the absence of working examples that correlate with the claimed invention, the skilled artisan will be forced to engage in experimentation to develop therapeutic methods and pharmaceutical compositions that meet the limits of the claims. The experimentation will include developing therapeutic methods and compositions that deliver the required amount of the antisense expression vector or antisense oligonucleotide of the invention to a pre-existing tumor in a whole animal. Given the undeveloped state of the therapeutic nucleic acid art, the breadth of the claims, and the unpredictability of the art, such experimentation would be extensive and of a trial-and-error nature. Such experimentation can not be considered routine.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation. See MPEP § 2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging in undue experimentation, the specification fails to provide an enabling disclosure.

12. No claim is allowed.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 305-7939. It is recommended that the examiner be notified when a fax is sent to this number.

Any inquiry concerning this communication or earlier communications should be directed to Thom Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

Thomas G. Larson, Ph.D.
Examiner

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